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An expedient route to indoles via a cycloaddition/cyclization sequence from (*Z*)-1-methoxybut-1-en-3-yne and 2*H*-pyran-2-ones

Krištof Kranjc, Marijan Kočevar*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

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Abstract

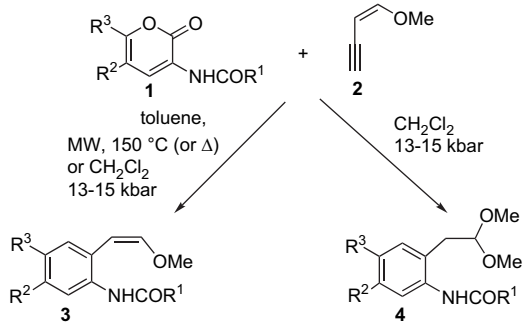
The cycloaddition of (*Z*)-1-methoxybut-1-en-3-yne (**2**) with 5,6-disubstituted 3-acylamino-2*H*-pyran-2-ones **1** under microwave-irradiation conditions, with classical heating or at high-pressures (13–15 kbar) affords the benzene derivatives **3** with a strategically positioned 2-methoxyethenyl moiety. In some cases, at high-pressures after long reaction times, 2,2-dimethoxyethyl products **4** were obtained. Adducts **3** and **4** can be cyclized under mild conditions into 1,5,6-trisubstituted indole derivatives **5**.

1. Introduction

The indole skeleton[1] occurs in many important natural products, pharmaceuticals, and other synthetic materials exhibiting a variety of biological activities and other properties. For example, 1*H*-indole-3-acetic acid is a plant-growth-regulating hormone,[1d,f] Indomethacin blocks prostaglandin biosynthesis,[1a,d,f] Cinmetacin is a nonsteroidal anti-inflammatory agent,[1c,f] Indoramin and Pindolol are antihypertensives,[1a,d,f] Ondasetron is an antiemetic,[1c,d,f] and Sumatriptan is an antimigraine.[1c,d,f] On the other hand, Indo-1 serves as a fluorescent probe for measuring the calcium in biological systems, etc. There are many methods for the preparation of indole systems, from classical techniques to those employing more recently discovered reactions, especially palladium-catalyzed transformations.[1,2] Functionalization of the indole skeleton at the positions 1, 2, and 3 can easily be achieved by standard procedures, whereas the preparation of indole systems with substituents on the benzene ring is, with a few exceptions, not very efficient. Among them, the syntheses of 1-acyl-5,6-disubstituted indoles with carbonyl containing groups on the benzene ring are very rare.[3]

2. Results and discussion

Here we report a short and convenient synthesis of 1-acyl-5,6-disubstituted indoles of type **5**, containing a methyl or substituted methyl group at position 5 and a carbonyl moiety at position 6, starting from 2*H*-pyran-2-one derivatives **1**[4] and (*Z*)-1-methoxybut-1-en-3-yne (**2**) (Schemes 1 and 2). Diels–Alder reactions of 2*H*-pyran-2-ones as dienes with alkynes have been often described as synthetically useful



Scheme 1. Cycloaddition of (*Z*)-1-methoxybut-1-en-3-yne (**2**) on 2*H*-pyran-2-ones **1** under microwave irradiation and high-pressure conditions.

* Corresponding author.
E-mail address: marijan.kocevar@fkkt.uni-lj.si (M. Kočevar).

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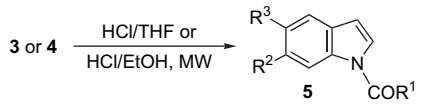


Scheme 2. Cyclization of cycloadducts **3** or **4** into indoles **5**.

reactions.[5] On the other hand, the use of **2** as a dienophile in any Diels–Alder reaction, to our knowledge, has not yet been published, but it has been used in another series of reactions.[6] We demonstrate here that it can be employed as an interesting dienophile for cycloadditions with substituted 2*H*-pyran-2-ones **1**. Based on the different electronic densities of both multiple bonds in **2**, we expected the cycloaddition to be chemoselective. A preferential reaction of the triple bond with a regioselectivity analogous to those previously observed[5d–f] for Diels–Alder reactions between alkynes and 2*H*-pyran-2-ones would generate interesting precursors for cyclization into substituted indoles and establish an efficient de novo synthesis of the indole system. Indeed, we found that the reaction between differently substituted 3-acylamino-2*H*-pyran-2-ones **1a–h** and (*Z*)-1-methoxybut-1-en-3-yne (**2**) after a short microwave irradiation[7] (45–180 min) at 150 °C affords cycloadducts (*Z*)-**3a–h** (Scheme 1, Table 1). In all cases we observed the formation of a single cycloadduct (by ^{1}H NMR spectrometry analysis of the crude reaction mixtures). All products **3** were of the same structural type, for the formation of which the triple bond had reacted preferentially in a completely regioselective way to give compounds containing the two hydrogen atoms on the aromatic ring *para* to one another.

The cycloaddition between (*Z*)-1-methoxybut-1-en-3-yne (**2**) and electron-rich 2*H*-pyran-2-ones (e.g., *N*-[5-(4-methoxyphenyl)-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamide, **1**: R^1=Ph, R^2=4-$MeOC_6H_4$, R^3=Me)[4f] or 2*H*-pyran-2-ones without any strong electron-withdrawing groups (e.g., *N*-(6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide, **1**: R^1=Ph, R^2=H, R^3=Me)[4e] even after prolonged microwave irradiation (for 4 h at 150 °C) did not yield any products and the starting materials were recovered. This suggests an inverse electron demand cycloaddition. Furthermore, it seems that the presence of at least one electron-withdrawing group on the starting 2*H*-pyran-2-one ring **1** is a prerequisite for these reactions to take place. The chemoselectivity and the regioselectivity might be controlled by the electron-donating properties of the methoxy group enhancing the nucleophilic character of the triple bond of the enyne **2**. On the other hand, the electron-withdrawing character of the 5-acyl (or 5-alkoxycarbonyl) moiety of the 2*H*-pyran-2-one **1** contributes to the at least partial stabilization of the negative charge in the 2*H*-pyran-2-one part in the transition state.[5e] These results complement an extensive study by Danishefsky's and Houk's groups, where the completely opposite situation was taken into consideration: i.e., the reaction between electron-rich dienes (substituted cyclohexa-1,3-dienes and buta-1,3-dienes) and enynes containing one or more electron-withdrawing ester functionalities.[8] It was shown that the Diels–Alder cycloaddition of the enynes occurred specifically at the triple bond and that its regiochemistry was apparently determined by the remote group bound at the olefinic site of the enyne.

We were also curious to find out if these cycloadditions would give the same products **3** when they were carried out under different conditions. Therefore, we tried with high-pressure conditions,[9] which are known to accelerate cycloaddition reactions due to the negative volume of activation. However, we found that in our case the high-pressure conditions (13–15 kbar) were only partially successful; the necessary reaction times in the dichloromethane solution were long (up to 36 days), and in some cases even after long reaction times the reactions were not yet complete (Table 2, run 6). In two cases, i.e., with **1a**,**b** (Table 2, runs 2 and 4) after an extremely long reaction time (138 days) a new reaction was observed and we were able to isolate products **4a**,**b** containing the 2,2-dimethoxyethyl moiety in their structure. Their appearance can be explained by the addition of a molecule of MeOH to the previously formed 2-methoxyethenyl moiety.

Furthermore, we explored the possibility of the cycloaddition between **1** and **2** under classical thermal conditions, where we observed the formation of the products **3** like under microwave irradiation, but the necessary reaction times were rather long. For example, for the synthesis of **3a** the necessary time of reflux in toluene was 5.5 h (as observed by TLC) and for the reaction between **1b** and **2** after 5 h of reflux in toluene, the conversion estimated from ^{1}H NMR of the crude reaction mixture was only around 60%.

Such cycloadducts **3** and **4** are perfectly suitable for the next step, i.e., the cyclization into indoles **5**. On the basis of

Table 1
Microwave-assisted cycloadditions of (*Z*)-1-methoxybut-1-en-3-yne (**2**) on 2*H*-pyran-2-ones **1**

Run	Starting **1**				t[a] (min)	Yield[b] (%)	Product **3**
	R^1	R^2	R^3				
1	Ph	COMe	Me	**1a**	90	80	**3a**
2	Ph	COPh	Me	**1b**	45	78	**3b**
3	Me	COMe	Me	**1c**	180	84	**3c**
4	CH_2Ph	COMe	Me	**1d**	120	78	**3d**
5	Ph	CO_2Me	CH_2CO_2Me	**1e**	120	76	**3e**
6	Ph	CO_2Et	CH_2CO_2Et	**1f**	120	82	**3f**
7	Ph	CO_2Me	Me	**1g**	120	76	**3g**
8	Ph	CO_2Et	Me	**1h**	135	69	**3h**

[a] Microwave irradiation, temperature set to 150 °C.
[b] Yields of isolated products.

Table 2
High-pressure cycloadditions of (*Z*)-1-methoxybut-1-en-3-yne (**2**) on 2*H*-pyran-2-ones **1**

Run	Starting **1**	t[a] (days)	Yield[b] (%)	Product
1	**1a**	15	78	**3a**
2	**1a**	138	77	**4a**
3	**1b**	17	87	**3b**
4	**1b**	138	74	**4b**
5	**1c**	36	81	**3c**
6	**1e**	29	2:1	**1e**:**3e**
7	**1h**	15	1:0	**1h**:**3h**

[a] At 13–15 kbar in CH_2Cl_2 at room temperature.
[b] Yields of isolated products.

the two previous papers, which report a related preparation of a few indole derivatives,[3a,b] we first tried with the conditions described therein. After 24 h of stirring cycloadducts **3** in an acidic THF solution (5% hydrochloric acid) and appropriate workup gave indoles **5a**,**b** in good yields (76 and 81%, respectively) (Scheme 2, Table 3).

Table 3
Cyclization of adducts **3** or **4** into indoles **5**

Run	Starting **3** or **4**	Yield[a] (%)	Product **5**
1	**3a**	82 (76)[b]	**5a**
2	**3b**	87 (81)[b]	**5b**
3	**3c**	85	**5c**
4	**3d**	72	**5d**
5	**3e**	82	**5e**
6	**3f**	78	**5f**
7	**3g**	76	**5g**
8	**3h**	71	**5h**
9	**4b**	79	**5b**

[a] Yields of isolated products after 10–15 min of microwave-irradiated reaction in acidified EtOH at 120 °C.
[b] Yields of isolated products after 24 h of reaction in acidified THF at room temperature.

We assumed that this reaction might be accelerated by submitting the reaction mixture to microwaves. Indeed, irradiation of a slurry of cycloadducts **3** or **4** in acidified EtOH at 120 °C for 10–15 min yielded indoles **5** in very good yields (Scheme 2, Table 3). This method represents the fastest route for the synthesis of the above products.

This reaction sequence for the production of indoles **5** can also be achieved as a one-pot-two-step transformation without the need for the isolating cycloadducts **3**. In these cases only diluted hydrochloric acid is added after the first cycloaddition step (carried out under microwave irradiation) directly to the reaction mixture and irradiation with microwaves at 150 °C is continued for another 10–15 min. The conversion starting from **1b** and **2** to the indole **5b**, for example, was complete (as proved by ^{1}H NMR spectra of the crude reaction mixtures), but due to some degradation products the isolation of **5b** is somewhat troublesome and the yields are consequently lower than in a two-step procedure (for **5b** 42% for the one-pot reaction vs 68% for the two steps).

3. Conclusion

We have developed an efficient, two-step synthesis of 1,5,6-trisubstituted indoles **5**. The first step is a microwave, thermal or high-pressure activated Diels–Alder cycloaddition reaction between (*Z*)-1-methoxybut-1-en-3-yne (**2**) and a series of 2*H*-pyran-2-ones **1** yielding appropriately substituted aniline derivatives **3** or **4**. The second step is a facile cyclization effected under mildly acidic conditions and accelerated by microwave irradiation to give indole derivatives **5** in an elegant way. It is also important to mention here[10] that in two cases different products were obtained under high-pressure conditions in comparison with microwave-assisted reactions.

4. Experimental

4.1. General

Melting points were determined on a Kofler micro hot stage and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 29 °C and 300 MHz using TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz and are referenced against the central line of the solvent signal ($CDCl_3$ triplet at δ=77.0 ppm). The coupling constants (J) are given in hertz. IR spectra were obtained with a Bio-Rad FTS 3000MX (KBr pellets for all products). MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin–Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica gel TLC-cards. The starting compounds **1a**,[4a] **1b**,[4b] **1c**,[4c] **1e**,[4d] **1h**,[4a] *N*-[5-(4-methoxyphenyl)-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamide (**1**: R^1=Ph, R^2=4-$MeOC_6H_4$, R^3=Me),[4f] and *N*-(6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (**1**: R^1=Ph, R^2=H, R^3=Me)[4e] were prepared according to the published procedures. *N*-(5-Acetyl-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-phenylacetamide (**1d**) was prepared from 5-acetyl-3-amino-6-methyl-2*H*-pyran-2-one[4c] and phenylacetyl chloride in CH_2Cl_2 using the method described for the synthesis of **1c**.[4c] Ethyl 3-(benzoylamino)-6-(ethoxycarbonyl)-methyl-2-oxo-2*H*-pyran-5-carboxylate (**1f**)[11] resulted from the reaction of diethyl 1,3-acetonedicarboxylate, diethoxymethyl acetate, hippuric acid, and acetic anhydride analogous to the synthesis of **1e**.[4d] Methyl 3-(benzoylamino)-6-methyl-2-oxo-2*H*-pyran-5-carboxylate (**1g**) was obtained from methyl acetoacetate, *N*,*N*-dimethylformamide dimethyl acetal, hippuric acid, acetic anhydride, and glacial acetic acid, analogous to the preparation of **1h**.[4a] All other reagents and solvents were used as received from commercial suppliers. Microwave reactions were conducted in air using a focused microwave unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused microwave power-delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel. The mixtures were stirred with a Teflon-coated magnetic stirring bar in the vessel. Temperature, pressure, and power profiles were recorded using commercially available software (ChemDriver 3.6.0) provided by the manufacturer of the microwave unit.

4.2. Microwave-assisted synthesis of *3*

A mixture of the starting 2*H*-pyran-2-one **1** (2 mmol) and (*Z*)-1-methoxybut-1-en-3-yne (**2**) (50% solution in MeOH) (8 mmol) in 3 mL of toluene was irradiated in the focused microwave equipment for the time specified (Table 1). The final temperature was set to 150 °C, the power to 120 W, and the

ramp time to 5 min. For typical temperature, pressure, and power profiles see Figure 1. Thereafter, the reaction mixture was cooled, the volatile components were removed in vacuo, the remaining solid was treated with MeOH (1.5 mL) and cooled. The precipitated product **3** was filtered off and washed with MeOH (1 mL).

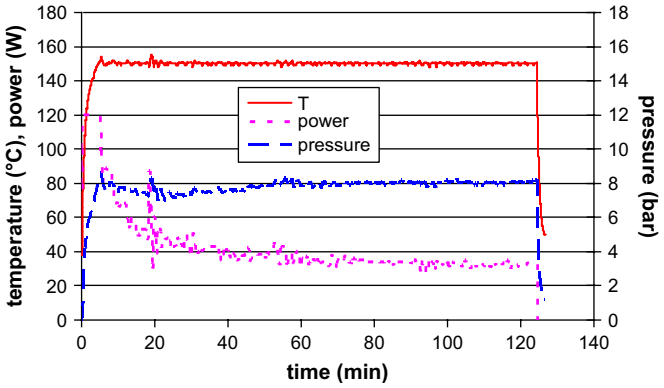


Figure 1. Typical temperature (red; ——), power (violet; ·····) and pressure (blue; — —) profiles for the microwave-assisted synthesis of **3f**.

4.3. High-pressure-assisted synthesis of *3* and *4*

A mixture of the starting 2*H*-pyran-2-one **1** (0.5 mmol) and (*Z*)-1-methoxybut-1-en-3-yne (**2**) (50% solution in MeOH) (2 mmol) in CH_2Cl_2 (3.8 mL) in a Teflon ampoule was immersed into a piston-cylinder type of pressure vessel filled with white spirit and pressurized at 13–15 kbar for the time specified (Table 2). The volatile components were then removed in vacuo and the remaining solid was treated with MeOH (0.5 mL) and cooled. The precipitated product **3** or **4** was filtered off and washed with MeOH (0.5 mL).

4.4. Synthesis of indoles *5*

4.4.1. Microwave conditions

To a suspension of the cycloadduct **3** (1 mmol) in EtOH (3 mL) hydrochloric acid (5%, 0.25 mL) was added and the reaction mixture was irradiated in the focused microwave equipment for 10–15 min. The final temperature was set to 120 °C, the power to 100 W, and the ramp time to 5 min (Table 3). Thereafter, the reaction mixture was cooled, the volatile components were removed in vacuo, the remaining solid was treated with EtOH (1 mL) and cooled. The precipitated product **5** was filtered off and washed with EtOH (0.5 mL).

4.4.2. At room temperature

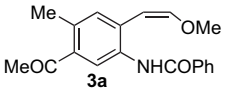
To a stirred solution of the cycloadduct **3** (1 mmol) in THF (12 mL) at room temperature hydrochloric acid (5%, 0.25 mL) was added (Table 3). The stirring was continued for 24 h, thereafter the volatile components were evaporated in vacuo, the remaining solid was treated with EtOH (1 mL) and cooled. The precipitated product **5** was filtered off and washed with EtOH (0.5 mL).

4.5. Two-step-one-pot synthesis of indole *5b*

A mixture of *N*-(5-benzoyl-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (**1b**) (666 mg, 2 mmol) and (*Z*)-1-methoxybut-1-en-3-yne (**2**) (50% solution in MeOH) (8 mmol) in 3 mL of toluene was irradiated in the focused microwave equipment for 45 min. The final temperature was set to 150 °C, the power to 120 W, and the ramp time to 5 min. Thereafter, the reaction mixture was cooled, hydrochloric acid (5%, 0.50 mL) was added and the reaction mixture was again irradiated in the focused microwave equipment for 15 min. The final temperature was set to 120 °C, the power to 100 W, and the ramp time to 5 min. Thereafter, the reaction mixture was cooled, the volatile components were removed in vacuo and from the remaining solid the product **5b** was obtained by column chromatography (eluent: light petroleum/AcOEt=3:1) as a pale-brown powder (285 mg, 42%).

4.6. Analytical and spectroscopic data of products

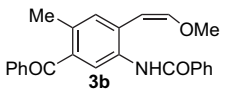
4.6.1. *N*-{5-Acetyl-2-[(*Z*)-2-methoxyethenyl]-4-methylphenyl}benzamide (*3a*)



3a

Mp 118–121 °C (MeOH). IR (KBr): 3126, 3188, 1677, 1643, 1601, 1557, 1516, 1489 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, Me), 2.62 (3H, s, Me), 3.80 (3H, s, OMe), 5.37 (1H, d, J=7.2 Hz), 6.25 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.23 (1H, s, 3-H or 6-H), 7.51 (3H, m, Ph), 7.88 (2H, m, Ph), 8.56 (1H, s, 3-H or 6-H), 8.69 (1H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 29.2, 60.9, 102.0, 125.3, 127.0, 128.6, 130.2, 131.7, 132.2, 133.2, 134.8, 135.2, 135.4, 147.8, 165.7, 200.8. MS: *m/z* 309 (M^+, 34%), 105 (100). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.93; H, 6.32; N, 4.65.

4.6.2. *N*-{5-Benzoyl-2-[(*Z*)-2-methoxyethenyl]-4-methylphenyl}benzamide (*3b*)

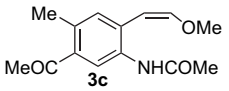


3b

Mp 174–176 °C (MeOH). IR (KBr): 3349, 1670, 1650, 1634, 1603, 1542, 1505, 1468 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (3H, s, Me), 3.80 (3H, s, OMe), 5.40 (1H, d, J=7.2 Hz), 6.24 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.32 (1H, s, 3-H or 6-H), 7.51 (6H, m, 2×Ph), 7.86 (4H, m, 2×Ph), 8.05 (1H, s, 3-H or 6-H), 8.62 (1H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.6, 60.9, 102.2, 124.7, 127.0, 128.4, 128.6, 129.2, 130.2, 131.6, 131.7, 132.4, 133.0, 133.4, 135.2, 136.7, 137.6, 147.6, 165.6, 197.6. MS: *m/z* 371

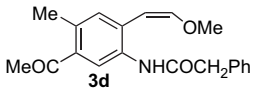
(M^+, 33%), 105 (100). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.40; H, 5.80; N, 3.71.

*4.6.3. N-{5-Acetyl-2-[(Z)-2-methoxyethenyl]-4-methylphenyl}acetamide (**3c**)*



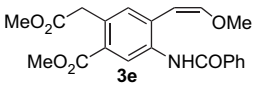
Mp 110–112 °C (MeOH). IR (KBr): 3269, 1679, 1655, 1605, 1561, 1521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (3H, s, Me), 2.48 (3H, s, Me), 2.57 (3H, s, Me), 3.84 (3H, s, OMe), 5.29 (1H, d, J=7.2 Hz), 6.24 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.26 (1H, s, 3-H or 6-H), 7.82 (1H, br s, NH), 8.37 (1H, s, 3-H or 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3, 24.3, 29.2, 60.9, 101.3, 125.4, 130.3, 131.9, 133.1, 134.8, 135.2, 148.4, 168.4, 200.8. MS: *m/z* 247 (M^+, 87%), 158 (100). HRMS (CI^+) calcd for $C_{14}H_{17}NO_3$ 247.1212, found 247.1208. Anal. Calcd for $C_{14}H_{17}NO_3 \times 0.1H_2O$: C, 67.51; H, 6.96; N, 5.62. Found: C, 67.58; H, 7.13; N, 5.40.

*4.6.4. N-{5-Acetyl-2-[(Z)-2-methoxyethenyl]-4-methylphenyl}-2-phenylacetamide (**3d**)*



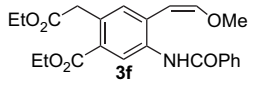
Mp 139.5–142 °C (EtOH). IR (KBr): 3251, 1678, 1652, 1605, 1553, 1516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (3H, s, Me), 2.57 (3H, s, Me), 3.56 (3H, s, OMe), 3.76 (2H, s, CH_2), 5.00 (1H, d, J=7.2 Hz), 5.99 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.21 (1H, s, 3-H or 6-H), 7.38 (5H, m, Ph), 7.58 (1H, br s, NH), 8.39 (1H, s, 3-H or 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3, 29.2, 44.9, 60.7, 100.5, 124.8, 127.5, 129.0, 129.6, 129.9, 131.8, 132.9, 134.6, 134.8, 135.2, 148.5, 169.3, 200.8. MS: *m/z* 323 (M^+, 55%), 91 (100). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.07; H, 6.73; N, 4.09.

*4.6.5. Methyl 5-(benzoylamino)-2-(methoxycarbonyl)-methyl-4-[(Z)-2-methoxyethenyl]-benzoate (**3e**)*



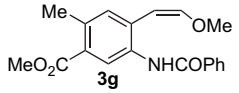
Mp 138–141 °C (MeOH). IR (KBr): 3270, 1737, 1712, 1642, 1607, 1514, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.70 (3H, s, Me), 3.80 (3H, s, Me), 3.86 (3H, s, Me), 3.99 (2H, s, CH_2), 5.37 (1H, d, J=7.3 Hz), 6.26 (1H, d, J=7.3 Hz, C*H*=C*H*OMe), 7.30 (1H, s, 3-H or 6-H), 7.52 (3H, m, Ph), 7.88 (2H, m, Ph), 8.62 (1H, br s, NH), 8.73 (1H, s, 3-H or 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 40.0, 51.86, 51.97, 61.0, 101.8, 126.4, 127.1, 127.9, 128.7, 131.1, 131.8, 132.1, 133.61, 133.69, 135.2, 148.2, 165.6, 167.0, 172.0. MS: *m/z* 383 (M^+, 12%), 105 (100). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.81; H, 5.46; N, 3.38.

*4.6.6. Ethyl 5-(benzoylamino)-2-(ethoxycarbonyl)-methyl-4-[(Z)-2-methoxyethenyl]benzoate (**3f**)*



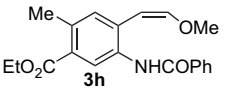
Mp 132–134 °C (EtOH). IR (KBr): 3259, 1734, 1711, 1649, 1608, 1515, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, J=7.1 Hz, CH_2CH_3), 1.37 (3H, t, J=7.1 Hz, CH_2CH_3), 3.79 (3H, s, Me), 3.98 (2H, s, CH_2CO_2Et), 4.15 (2H, q, J=7.1 Hz, CH_2CH_3), 4.33 (2H, q, J=7.1 Hz, CH_2CH_3), 5.37 (1H, d, J=7.2 Hz), 6.24 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.30 (1H, s, 3-H or 6-H), 7.52 (3H, m, Ph), 7.88 (2H, m, Ph), 8.60 (1H, br s, NH), 8.68 (1H, s, 3-H or 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.12, 14.18, 40.2, 60.5, 60.8, 60.9, 101.6, 126.5, 127.0, 128.3, 128.6, 131.1, 131.7, 132.0, 133.4, 133.5, 135.1, 148.2, 165.6, 166.6, 171.5. MS: *m/z* 411 (M^+, 10%), 105 (100). Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.11; H, 6.28; N, 3.28.

*4.6.7. Methyl 5-(benzoylamino)-4-[(Z)-2-methoxyethenyl]-2-methylbenzoate (**3g**)*



Mp 108–110 °C (EtOH). IR (KBr): 3414, 1716, 1647, 1617, 1522, 1488 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.58 (3H, s, Me), 3.80 (3H, s, Me), 3.87 (3H, s, Me), 5.37 (1H, d, J=7.2 Hz), 6.24 (1H, d, J=7.2 Hz, C*H*=C*H*OMe), 7.28 (1H, s, 3-H or 6-H), 7.51 (3H, m, Ph), 7.88 (2H, m, Ph), 8.59 (1H, br s, NH and 6-H or 3-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2, 51.6, 60.9, 101.8, 126.3, 127.0, 127.6, 128.5, 131.1, 131.6, 132.1, 132.8, 135.1, 136.5, 147.9, 165.6, 167.3. MS: *m/z* 325 (M^+, 34%), 105 (100). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.14; H, 5.89; N, 4.21.

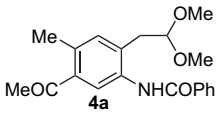
*4.6.8. Ethyl 5-(benzoylamino)-4-[(Z)-2-methoxyethenyl]-2-methylbenzoate (**3h**)*



Mp 129–131 °C (EtOH). IR (KBr): 3196, 2980, 1724, 1643, 1607, 1558, 1523 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, t, J=7.2 Hz, CH_2CH_3), 2.57 (3H, s, Me), 3.79 (3H, s, OMe), 4.34 (2H, q, J=7.2 Hz, CH_2CH_3), 5.36 (1H, d, J=7.1 Hz), 6.22 (1H, d, J=7.1 Hz, C*H*=C*H*OMe), 7.29 (1H, s, 3-H or 6-H), 7.51 (3H, m, Ph), 7.88 (2H, m, Ph), 8.55 (2H, br s, NH and 6-H or 3-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2, 21.2, 60.5, 60.9, 101.8, 126.3, 127.0, 128.1, 128.6, 131.1, 131.6, 132.1, 132.8, 135.1, 136.4, 147.9, 165.7, 167.0. MS: *m/z* 339 (M^+, 36%), 105 (100). Anal. Calcd

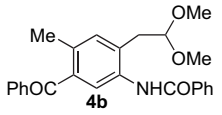
for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.77; H, 6.25; N, 4.05.

*4.6.9. N-[5-Acetyl-2-(2,2-dimethoxyethyl)-4-methylphenyl]benzamide (**4a**)*



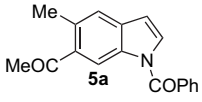
Mp 122.5–125 °C (MeOH). IR (KBr): 3376, 3341, 1682, 1663, 1571, 1515, 1481 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (3H, s, Me), 2.62 (3H, s, Me), 2.99 (2H, d, J=5.1 Hz, CH_2), 3.47 (6H, s, 2×OMe), 4.53 (1H, t, J=5.1 Hz, C*H*$(OMe)_2$), 7.08 (1H, s, 3-H or 6-H), 7.53 (3H, m, Ph), 7.96 (2H, m, Ph), 8.54 (1H, s, 3-H or 6-H), 9.61 (1H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1, 29.4, 37.1, 54.8, 106.8, 125.2, 127.1, 128.7, 131.3, 131.8, 134.66, 134.79, 134.85, 134.87, 136.3, 165.4, 201.1. MS: *m/z* 341 (M^+, 5%), 75 (100). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.32; H, 6.99; N, 4.03.

*4.6.10. N-[5-Benzoyl-2-(2,2-dimethoxyethyl)-4-methylphenyl]benzamide (**4b**)*



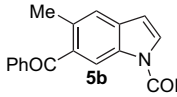
Mp 133–135 °C (MeOH). IR (KBr): 3350, 1673, 1659, 1578, 1525 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 3.02 (2H, d, J=5.2 Hz, CH_2), 3.49 (6H, s, 2×OMe), 4.56 (1H, t, J=5.2 Hz, C*H*$(OMe)_2$), 7.15 (1H, s, 3-H or 6-H), 7.44–7.60 (6H, m, 2×Ph), 7.91 (4H, m, 2×Ph), 8.06 (1H, s, 3-H or 6-H), 9.57 (1H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.4, 37.1, 54.7, 106.9, 124.4, 127.0, 128.4, 128.6, 130.1, 130.3, 131.7, 133.1, 133.3, 133.8, 134.4, 134.7, 137.4, 137.5, 165.2, 197.7. MS: *m/z* 403 (M^+, 3%), 75 (100). Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.38; H, 6.43; N, 3.38.

*4.6.11. 1-(1-Benzoyl-5-methyl-1H-indol-6-yl)ethanone (**5a**)*



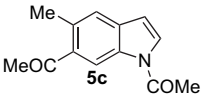
Mp 145–147 °C (EtOH). IR (KBr): 1680, 1615, 1599, 1567, 1521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (3H, br s, Me), 2.67 (3H, s, Me), 6.58 (1H, dd, $J_1 \approx 0.7$ Hz, J_2=3.8 Hz, 3-H), 7.43 (1H, d, J=3.8 Hz, 2-H), 7.45 (1H, dd, $J_1 \approx J_2 \approx 0.7$ Hz, 7-H), 7.55 (2H, m, Ph), 7.64 (1H, m, Ph), 7.75 (2H, m, Ph), 8.82 (1H, d, $J \approx 0.7$ Hz, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.1, 29.5, 108.1, 118.2, 123.6, 128.7, 129.1, 130.4, 132.1, 133.3, 133.8, 134.2, 134.4, 134.5, 168.5, 201.4. MS: *m/z* 277 (M^+, 37%), 105 (100). HRMS (CI^+) calcd for $C_{18}H_{15}NO_2$ 277.1108, found 277.1103. Anal. Calcd for $C_{18}H_{15}NO_2 \times 0.1H_2O$: C, 77.46; H, 5.49; N, 5.02. Found: C, 77.38; H, 5.58; N, 4.90.

*4.6.12. (1-Benzoyl-5-methyl-1H-indol-6-yl)(phenyl)-methanone (**5b**)*



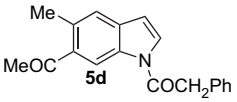
Mp 111.5–114 °C (EtOH). IR (KBr): 1681, 1662, 1594, 1578, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (3H, s, Me), 6.61 (1H, d, J=3.2 Hz, 3-H), 7.48 (8H, m), 7.71 (2H, m), 7.85 (2H, m) (2×Ph, 2-H, 7-H), 8.38 (1H, br s, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3, 108.1, 117.1, 122.8, 128.4, 128.6, 129.1, 129.5, 130.3, 132.0, 132.4, 132.8, 133.0, 133.4, 134.2, 135.6, 138.1, 168.4, 198.6. MS: *m/z* 339 (M^+, 29%), 105 (100). HRMS (CI^+) calcd for $C_{23}H_{17}NO_2$ 339.1252, found 339.1259. Anal. Calcd for $C_{23}H_{17}NO_2 \times 1/4H_2O$: C, 80.33; H, 5.13; N, 4.07. Found: C, 80.46; H, 5.20; N, 4.05.

*4.6.13. 1-(1-Acetyl-5-methyl-1H-indol-6-yl)ethanone (**5c**)*



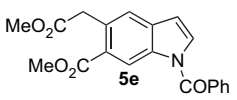
Mp 114–116 °C (EtOH). IR (KBr): 1710, 1666, 1612, 1565, 1520, 1472, 1458 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.61 (3H, s, Me), 2.65 (3H, s, Me), 2.67 (3H, s, Me), 6.60 (1H, dd, $J_1 \approx 0.9$ Hz, J_2=3.7 Hz, 3-H), 7.40 (1H, dd, $J_1 \approx J_2 \approx 0.9$ Hz, 7-H), 7.51 (1H, d, J=3.7 Hz, 2-H), 8.89 (1H, d, $J \approx 0.9$ Hz, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.0, 23.7, 29.5, 108.6, 118.3, 123.5, 128.0, 132.8, 133.4, 134.0, 134.6, 168.5, 201.5. MS: *m/z* 215 (M^+, 42%), 158 (100). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.73; H, 6.37; N, 6.55.

*4.6.14. 1-[5-Methyl-1-(phenylacetyl)-1H-indol-6-yl]-ethanone (**5d**)*



Mp 112–114 °C (EtOH). IR (KBr): 1687, 1681, 1618, 1569, 1525 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (3H, s, Me), 2.66 (3H, s, Me), 4.28 (2H, s, CH_2), 6.61 (1H, d, J=3.6 Hz, 3-H), 7.37 (6H, m, Ph, 7-H), 7.63 (1H, d, J=3.6 Hz, 2-H), 8.96 (1H, s, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.0, 29.5, 42.7, 108.9, 118.5, 123.5, 127.5, 128.9, 129.1, 132.7, 133.0, 133.6, 134.3, 134.6, 169.3, 201.4 (one signal is hidden). MS: *m/z* 291 (M^+, 48%), 158 (100). HRMS (EI^+) calcd for $C_{19}H_{17}NO_2$ 291.1266, found 291.1259. Anal. Calcd for $C_{19}H_{17}NO_2 \times 1/4EtOH$: C, 77.33; H, 6.16; N, 4.62. Found: C, 77.55; H, 6.07; N, 4.34.

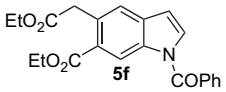
*4.6.15. Methyl 1-benzoyl-5-(methoxycarbonyl)methyl-1H-indole-6-carboxylate (**5e**)*



Mp 169.5–172 °C (EtOH). IR (KBr): 1745, 1707, 1679, 1531, 1468 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (3H,

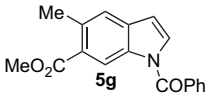
s, Me), 3.90 (3H, s, Me), 4.12 (2H, s, CH_2), 6.61 (1H, dd, $J_1 \approx 0.6$ Hz, $J_2=3.6$ Hz, 3-H), 7.45 (1H, d, $J=3.6$ Hz, 2-H), 7.48 (1H, br s, 7-H), 7.55 (2H, m, Ph), 7.64 (1H, m, Ph), 7.74 (2H, m, Ph), 9.08 (1H, br s, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 40.8, 51.9, 52.0, 108.0, 119.5, 124.2, 126.0, 128.7, 129.2, 130.7, 131.5, 132.2, 133.7, 134.0, 134.7, 167.8, 168.3, 172.4. MS: *m/z* 351 (M^+, 6%), 105 (100). HRMS (EI^+) calcd for $C_{20}H_{17}NO_5$ 351.1110, found 351.1107. Anal. Calcd for $C_{20}H_{17}NO_5 \times 1/3H_2O$: C, 67.23; H, 4.98; N, 3.92. Found: C, 67.41; H, 5.05; N, 3.58.

*4.6.16. Ethyl 1-benzoyl-5-(ethoxycarbonyl)-methyl-1H-indole-6-carboxylate (**5f**)*



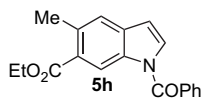
Mp 105–107 °C (EtOH). IR (KBr): 1734, 1706, 1682, 1528, 1467 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, $J=7.1$ Hz, CH_2CH_3), 1.38 (3H, t, $J=7.1$ Hz, CH_2CH_3), 4.12 (2H, s, CH_2CO_2Et), 4.17 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.35 (2H, q, $J=7.1$ Hz, CH_2CH_3), 6.61 (1H, dd, $J_1 \approx 0.8$ Hz, $J_2=3.8$ Hz, 3-H), 7.46 (1H, d, $J=3.8$ Hz, 2-H), 7.47 (1H, br s, 7-H), 7.54 (2H, m, Ph), 7.63 (1H, m, Ph), 7.74 (2H, m, Ph), 9.00 (1H, br s, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 14.2, 40.9, 60.5, 60.8, 108.0, 119.2, 124.0, 126.5, 128.6, 129.1, 130.4, 131.4, 132.1, 133.5, 133.9, 134.6, 167.3, 168.2, 171.8. MS: *m/z* 379 (M^+, 4%), 105 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.64; H, 5.54; N, 3.49.

*4.6.17. Methyl 1-benzoyl-5-methyl-1H-indole-6-carboxylate (**5g**)*



Mp 126–128 °C (EtOH). IR (KBr): 1716, 1679, 1618, 1598, 1574, 1528, 1466, 1451, 1435 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (3H, s, Me), 3.90 (3H, s, Me), 6.54 (1H, d, $J=3.7$ Hz, 3-H), 7.38 (1H, d, $J=3.7$ Hz, 2-H), 7.42 (1H, br s, 7-H), 7.56 (3H, m, Ph), 7.72 (2H, m, Ph), 8.97 (1H, br s, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.9, 51.7, 107.8, 118.8, 123.0, 126.2, 128.6, 129.1, 130.2, 132.0, 133.6, 133.8, 134.1, 135.6, 168.17, 168.21. MS: *m/z* 293 (M^+, 33%), 105 (100). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.47; H, 5.16; N, 4.70.

*4.6.18. Ethyl 1-benzoyl-5-methyl-1H-indole-6-carboxylate (**5h**)*



Mp 106.5–108 °C (EtOH). IR (KBr): 3414, 1707, 1692, 1618, 1571, 1529, 1466, 1456 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, t, $J=7.1$ Hz, CH_2CH_3), 2.70 (3H, s, Me), 4.38 (2H, q, $J=7.1$ Hz, CH_2CH_3), 6.57 (1H, dd, $J_1 \approx 0.7$ Hz, $J_2=3.8$ Hz, 3-H), 7.41 (1H, d, $J=3.8$ Hz, 2-H), 7.44 (1H, dd, $J_1 \approx J_2 \approx 0.7$ Hz, 7-H), 7.57 (3H, m, Ph), 7.73 (2H, m, Ph), 8.90 (1H, d, $J \approx 0.7$ Hz, 4-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 21.9, 60.6, 107.9, 118.6, 123.0, 126.7, 128.6, 129.1, 130.1, 132.0, 133.5, 133.8, 134.2, 135.4, 167.8, 168.2. MS: *m/z* 307 (M^+, 33%), 105 (100). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.96; H, 5.60; N, 4.49.

Acknowledgements

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References and notes

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